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Del(10)(q22.3q24.1) Associated With Juvenile Polyposis

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Juvenile polyps are the most frequent gastrointestinal polyps with a malignant potential for which the genetic basis is unknown. Juvenile polyps, with a normal epithelium but hypertrophic lamina propria, are histologically quite distinct from adenomatous polyps which have dysplastic changes in epithelial nuclei. Furthermore, the adenomatous polyposis coli (APC) gene on Chr 5, mutated somatically in adenomatous polyps and mutated in the germline of patients with familial adenomatous polyposis, is not linked to hereditary juvenile polyposis. We provide the first report indicating that a tumor suppressor gene associated with juvenile polyposis may be located at 10q22.3q24.1. Cytogenetic studies of a patient with juvenile polyposis and multiple congenital abnormalities of the head, extremities, and abdomen revealed a de novo interstitial deletion of Chr 10 as the only defect, del(10)(10q22.3q24.1). Am. J. Med. Genet. 70:361–364, 1997. © 1997 Wiley-Liss, Inc.

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INTRODUCTION

Solitary juvenile polyps are diagnosed in approximately 1% of children and account for most gastrointestinal polyps found before adulthood [Horrilleno et al., 1957; Heiss et al., 1993]. Although sporadic (solitary) polyps are common, the hereditary form of juvenile polyposis is relatively infrequent. The hereditary syndrome is characterized by multiple juvenile polyps or juvenile polyps in more than one relative. These polyps may be restricted to the colon ("juvenile polyposis coli") or may also affect the stomach or small intestine ("generalized juvenile gastrointestinal polyposis") [Sachatello et al., 1970; Sachatello and Griffen, 1975]. An autosomal dominant pattern of inheritance has been observed, Mendelian Inheritance in Man 174900 [McKusick, 1992]. Although the genetic basis of this syndrome is unknown, the distinctive histopathological characteristics of the polyps, and exclusion of linkage to APC gene markers [Leggett et al., 1993], support the hypothesis that hereditary juvenile polyposis is distinct from familial adenomatous polyposis.

Juvenile polyps are characterized by an abundant lamina propria which lacks smooth muscle proliferation and contains cystically dilated mucin-filled glands lined by a typically normal epithelium [Jass et al., 1988]. This is in sharp contrast to adenomatous polyps which have dysplastic changes involving the epithelium. Juvenile polyps were originally described as entirely benign lesions without malignant potential [Horrilleno et al., 1957; Morson, 1962; Roth and Helwig, 1963; McColl et al., 1964; Veale et al., 1966], but recent literature has indicated that patients with hereditary juvenile polyposis are at increased risk for adenocarcinoma of the gastrointestinal tract [Stemper et al.,1975; Jarvinen and Franssila, 1984; Giardiello et al., 1991; Heiss et al., 1993]. Reports of adenomatous change as well as adenocarcinoma associated with juvenile polyps suggest that these neoplasms arise from a dysplastic area that develops within a polyp [Kaschula, 1971; Goodman et al.,1979; Lipper et al.,1981; Jass et al.,1988]. Thus, this neoplastic progression recapitulates in its later stages the process that occurs commonly in malignant transformation of purely adenomatous polyps of the colon. However, we hypothesize that the initial genetic alteration in juvenile polyps involves inactivation of a novel tumor suppressor gene.

While surveying juvenile polyps for somatic loss of heterozygosity, we were fortunate to discover a unique patient with a germline abnormality particularly useful for mapping the chromosomal location of a putative

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juvenile polyposis gene. This patient had several different congenital defects and juvenile polyposis. The multiplicity of defects had suggested that a grossly evident constitutional chromosomal abnormality might be present. Cytogenetic analysis clearly demonstrated an interstitial deletion of chromosome 10q22.3-q24.1 as the sole abnormality. This observation provides the first evidence for a juvenile polyposis tumor suppressor gene locus at 10q22.3-q24.1.

METHODS AND RESULTS

Clinical Characterization

The patient was born at 36 weeks of gestation after an uncomplicated pregnancy and normal spontaneous vaginal delivery at another hospital. The parents were healthy and nonconsanguineous, with no apparent exposure by the mother (age 25 years) or father (age 27 years) to hazardous agents known to be genotoxic. Family history (parents, grandparents, 2 sibs, 2 maternal aunts, 2 maternal uncles, and 3 cousins) was unremarkable. Evaluation of the neonate included cranial ultrasound, head CT scan, and chest film, which were all normal. A club foot deformity was present. Results of routine blood counts and serum biochemistry tests were normal. He had surgical correction of the club feet with bilateral posteromedial releases and Achilles tendon lengthening with capsulotomy of the ankle and subtalar joints.

He was referred to the University of Wisconsin genetics clinic at age 10 months, where he appeared mildly abnormal overall, with a weight of 8.1 kg (~8th%), a height of 66.7 cm (<5th%), broad nasal apex and long philtrum, widely spaced canthi, hypoplastic ears (35 and 37 mm), small but proportionate head circumference of 42.8 cm (2nd%), and redundant neck skin. A mild systolic heart murmur was heard at the left 3rd intercostal space; an echocardiogram later demonstrated tricuspid insufficiency. A small umbilical hernia in the abdomen, hypoplastic oblique muscles with bilateral abdominal bulging laterally, and prominent venous patterning on thorax and abdomen were present. The hands and feet were plump dorsally. The feet were short and broad with crowded toes, and the patient required orthopedic shoes after surgical correction of club feet. The hands were short and broad with short distal phalanges and redundant skin. His growth was below normal, initially above the 15th centile for height, weight, and head circumference, and later falling below the 5th centile for each measure. His motor and language skills as assessed by the Denver test were developmentally delayed.

Endoscopy

The patient was referred to the University of Wisconsin Gastroenterology Clinic at age 4 years for evaluation of a 1-year history of hematochezia. At that time blood count showed a microcytic anemia with a hematocrit of 26% and MCV of 73 μm^3 (normal 81–99). Colonoscopy showed several dozen polyps distributed throughout the colon. The largest polyps (1.0–2.5 cm) were removed by snare polypectomy and diagnosed as juvenile polyps by histopathology. Repeat colonoscopy performed one year later for recurrent hematochezia showed more juvenile polyps (up to 2 cm diameter) and approximately 20 of the largest were cauterized or removed by snare electrosurgical technique.

Histopathology

Gross examination showed pedunculated and spherical polyps, usually with a smooth reddish surface and patches of yellowish mucus. Microscopic examination of hematoxylin and eosin stained formalin-fixed paraffin-embedded tissue sections was performed. The typical histological changes of juvenile polyps were present in each, none of which demonstrated dysplasia or adenomatous characteristics. The diagnosis of juvenile polyps was confirmed by a second pathologist.

Cytogenetic Analysis

Metaphase cultures from peripheral leukocytes were analyzed with a standard Giemsa method (Fig. 1). Mitotic cells in prometaphase and late prophase were derived from phytohemagglutinin stimulated lymphocytes by using standard 72-hour blood cultures and ethidium bromide treated cultures. Giemsa-banded preparations for 20 cells were examined in detail under the microscope to analyze chromosome number and structure, and for 3 cells a formal karyotype and photographs were prepared. All 20 cells counted had a normal diploid chromosome number of 46. However, an interstitial deletion in the long arm of chromosome number 10 was observed in one chromosome in each cell, pter→q22.3::q24.1→qter (Figs. 1 and 2). The karyotype of the patient was thus 46,XY,del(10)(q22.3q24.1).

The interstitial deletion was apparently de novo because the parents had normal chromosomes. Consistent with their normal karyotype, the parents had no evidence of juvenile polyposis or any other clinically evident abnormalities.

DISCUSSION

We report here an individual with a rare interstitial deletion of 10q, multiple congenital abnormalities, and juvenile polyposis. These findings provide the first evidence for a tumor suppressor gene at 10q22.3q24.1 that may be associated with juvenile polyposis.

The apoptosis-signaling receptor gene *FAS* maps within the deleted interval (Human Genome Database) and is a plausible candidate because failure of that function might result in a phenotype of benign polyp

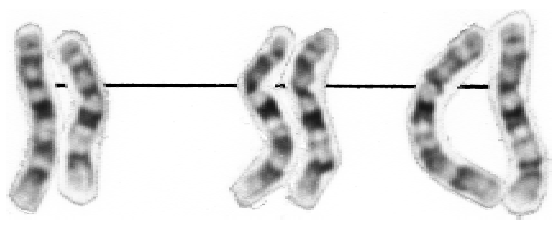

Fig. 1. Partial karyotype of the propositus showing normal chromosome 10 and the del(10)(q22.3q24.1).

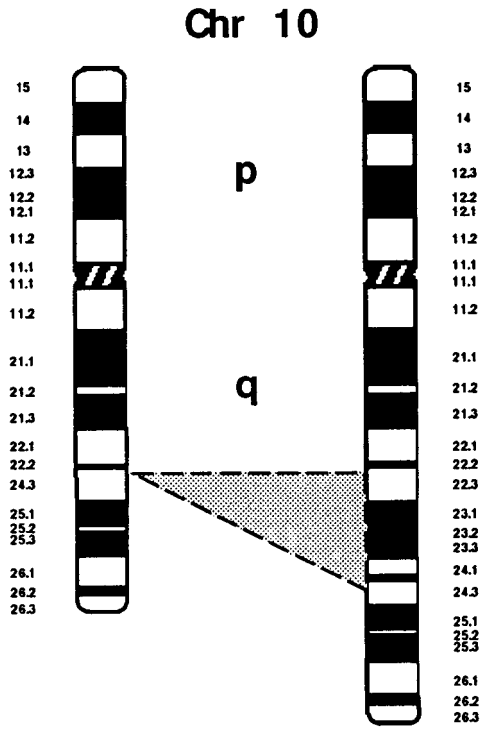

Fig. 2. Idiograms of normal chromosome 10 (**right**), and the patient's chromosomal abnormality (**left**) representing the interstitial deletion of q22.3-q24.1.

growth. Identification of the JP gene could provide important insights regarding the development of the neoplastic phenotype and factors affecting the maintenance of normal differentiation and interactions between the epithelium and submucosal tissues. The deleted interval that we have identified spans approximately 25 cM on chromosome 10 and should facilitate fine structure linkage analysis in affected families, or somatic deletion studies in juvenile polyps. A similar process led to the identification of the adenomatous polyposis gene (APC) after an interstitial deletion of Chr 5q was found by cytogenetic analysis of a patient with multiple congenital defects and Gardner's syndrome [Herrera et al., 1986].

Histopathological studies demonstrating dysplastic foci in some juvenile polyps suggest that an adenomatous intermediate may occur in some patients, which could then progress to colon cancer as in the Vogelstein model. However, the molecular mechanism underlying the increased risk for malignancy of the gastrointestinal tract in patients with juvenile polyposis is not yet known. If the putative JP gene functions as a tumor suppressor gene, allele losses at this locus should be frequent in juvenile polyps and might also be observed in colon carcinomas. Previous cytogenetic studies in a series of 26 colon carcinomas showed 10q loss or translocation in 16% of tumors with chromosomal aberrations [Reichmann et al., 1981]. However, deletion of many chromosome arms occurs commonly in aneuploid colon carcinomas. Loss of heterozygosity for genetic markers on Chr 10q was found in only 13% of colon carcinomas in another allelotype study, similar to the background rate of loss of chromosomal arms [Vogelstein et al., 1989]. Reports of small deletions may provide more specific map information. Deletions of 10q24 were observed in gastric and other adenocarcinomas, and deletion of 10q23q25 was found in a colon carcinoma [VanDerRiet-Fox et al., 1979; Muleris et al., 1987]. Relatively infrequent loss of alleles at this locus on Chr 10 would be consistent with the clinical impression that only a minority of colon carcinomas arise from juvenile polyps. Somatic loss of heterozygosity for a probe on chromosome 10q has recently been demonstrated by fluorescence in situ hybridization (FISH) analysis in most of juvenile polyps from a small series of patients, supporting the hypothesis that the congenital deletion we are reporting here is of pathogenetic significance [Jacoby et al., 1997].

The present report is the first to describe a chromosomal anomaly in a patient who had hereditary juvenile polyposis. Although a few cases of interstitial deletion of 10q have been described, none of the deletions involved exactly the same region as the present case and were associated with somewhat different clinical syndromes. The malformations in the previous patients included abnormalities of the head and limbs similar to those in our case, but none was diagnosed with juvenile polyposis [Shapiro et al., 1985; Gorinati et al., 1989; Wulfsberg et al., 1989; Lobo et al., 1992; Farrell et al., 1993]. The large deletion in our patient undoubtedly involves many genes, the subset overlapping the other cases probably responsible for the shared phenotypes. The lack of juvenile polyposis in cases with similar deletions could be the result of decreased penetrance caused by differences in the retained JP alleles or unlinked modifying loci, or the deletions may not have included the JP locus in each case. Other syndromes associated with hamartomatous polyps similar to those observed in our patient include the Ruvalcaba-Myhre-Smith syndrome and Cowden disease. A recent report [Nelen et al., 1996] demonstrates linkage of Cowden disease in several families to 10q22-23, an interval that overlaps the deletion identified here. Further investigation should determine the significance of this Chr 10 locus in the pathogenesis of juvenile polyps, and clarify the possible phenotypic or genotypic relationships between the various disorders that manifest with hamartomatous polyps.

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REFERENCES

Farrell SA, Szymonowicz W, Chow G, Summers AM (1993): Interstitial deletion of chromosome 10q23: a new case and review. J Med Genet 30:248–250.

Giardiello FM, Hamilton SR, Kern SE, Johan G, Offerhaus A, Green PA, Celano P, Krush AJ, Booker SV (1991): Colorectal neoplasia in juvenile polyposis or juvenile polyps. Arch Dis Child 66:971–975.

Goodman ZD, Yardley JH, Milligan FD (1979): Pathogenesis of colonic polyps in multiple juvenile polyposis. Cancer 43:1906–1913.

Gorinati M, Zamboni G, Padoin N, Dodero A, Caufin D, Memo L (1989): Brief clinical report: Terminal deletion of the long arm of chromosome 10: Case report and review of the literature. Am J Med Genet 33:502–504.

Heiss KF, Schaffner D, Ricketts RR, Winn K (1993): Malignant risk in juvenile polyposis coli: ncreasing documentation in the pediatric age group. J Pediatr Surg 8:1188–1193.

Herrera L, Kakati S, Gibas L, Pietrzak E, Sandberg AA (1986): Brief clinical report: gardner syndrome in a man with an interstitial deletion of 5q. Am J Med Genet 25:473–476.

Horrilleno EG, Eckert C, Ackerman LV (1957): Polyps of the rectum and colon in children. Cancer 10:1210–1220.

Jacoby RF, Schlack S, Cole CE, Marshall DJ, Kuhlman G, Sekhon G, Laxova R, Skarbeck M, Harris C, Meisner L (1997): Identification of a juvenile polyposis tumor suppressor gene locus (JP1) and demonstration of its deletion in sub-epithelial cells. Gastroenterology 112:1398–1403.

Jarvinen H, Franssila KO (1984): Familial juvenile polyposis coli: Increased risk of colorectal cancer. Gut 25:792–800.

Jass JR, Williams CB, Bussey HJR, Morson BC (1988): Juvenile polyposis: A precancerous condition. Histopathology 13:619–630.

Kaschula RO (1971): Mixed juvenile adenomatous and intermediate polyposis coli. Dis Colon Rectum 14:368–374.

Leggett BA, Thomas LR, Knight N, Healey S, Chenevix-Trench G, Searle J (1993): Exclusion of APC and MCC as the gene defect in one family with familial juvenile polyposis. Gastroenterology 105:1313–1316.

Lipper S, Kahn LB, Sandler RS, Varma V (1981): Multiple juvenile polyposis: A study of the pathogenesis of juvenile polyps and their relationships to the colonic adenomas. Hum Pathol 12:804–813.

Lobo S, Cervenka J, London A, Pierpont MEM (1992): Interstitial deletion of 10q: Clinical features and literature review. Am J Med Genet 43: 701–703.

McColl I, Bussey HJR, Veale AMO, Morson BC (1964): Juvenile polyposis coli. Proc R Soc Med 57:896–897.

McKusick VA (1992): "Mendelian Inheritance in Man, Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes," 10th ed. Baltimore: Johns Hopkins University Press.

Morson BC (1962): Some peculiarities in the histology of intestinal polyps. Dis Colon Rectum 5:337–344.

Muleris M, Salmon R, Dutrillaux A, Viehl P, Zafrani B, Girodet J, Dutrillaux B (1987): Characteristic chromosomal imbalances in 18 near-diploid colorectal tumors. Cancer Genet Cytogenet 29:289–301.

Nelen MR, Padberg GW, Peeters EAJ, Liu AY, Vanden Helm B, Frants RR, Coulon V, Goldstein AM, van Reen MMM, Easton DF, Eeles RA, Hodgson S, Mulvihill JJ, Murday VA, Tucker MA, Mariman ECM, Starink TM, Ponder BAJ, Ropers HH, Kremer H, Longy M, Eng C (1996): Localization of the gene for Cowden disease to chromosome 10q22-23. Nature Genet 13:114–116.

Reichmann A, Martin P, Levin B (1981): chromosomal banding patterns in human large bowel cancer. Int J Cancer 28:431–440.

Roth SI, Helwig EB (1963): Juvenile polyps of the colon and rectum. Cancer 16:468–479.

Sachatello CR, Griffen WO (1975): Hereditary polypoid disease of the gastrointestinal tract: A working classification. Am J Surg 129:198–203.

Sachatello CR, Pickren JW, Grace JT (1970): Generalized juvenile gastrointestinal polyposis: A hereditary syndrome. Gastroenterology 58:699–708.

Shapiro SD, Hansen KL, Pasztor LM, DiLiberti JH, Jorgenson RJ, Young RS, Moore CM (1985): Deletions of the long arm of chromosome 10. Am J Med Genet 20:181–196.

Stemper TJ, Kent TH, Summers RW (1975): Juvenile polyposis and gastrointestinal carcinoma: A study of a kindred. Ann Intern Med 83:639–646.

VanDerRiet-Fox M, Retief A, Niekerk W (1979): Chromosome changes in 17 human neoplasms studied with banding. Cancer 44:2108–2119.

Veale AMO, McColl I, Bussey HJR, Morson BC (1966): Juvenile polyposis coli. J Med Genet 3:5–16.

Vogelstein B, Fearon ER, Kern SE, Hamilton SR, Preisinger AC, Nakamura Y, White R (1989): Allelotype of colorectal carcinomas. Science 244:207–211.

Wulfsberg EA, Weaver RP, Cunniff CM, Jones MC, Jones KL (1989): Chromosome 10qter deletion syndrome: A review and report of three new cases. Am J Med Genet 32:364–367.